DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on February 16, 2010 has been entered.

2. Claims 1 and 4-33 were previously pending, with claims 4, 6, 7, 9, 11, 12, 14, 15, 18, 20 and 22-29 withdrawn from consideration. Applicants amended claims 1 and 30. Claims 1, 5, 8, 10, 13, 16, 17, 19, 21 and 30-33 will be examined.

3. Applicants' amendments overcame all of the previously presented rejections. This office action contains new grounds for rejection necessitated by amendment.

Claim Interpretation

4. Applicants described the term "nucleosomal polynucleotide" on page 8, paragraph [0025], as follows:

"As used herein, a "nucleosomal polynucleotide" includes any nucleic acid associated with histone core proteins, or histone-like core proteins, forming a chromatin-like structure." Therefore, it is interpreted as any nucleic acid associated with histones or other proteins, as Applicants did not define the terms "histone-like core-proteins" or "chromatin-like structure".

5. Applicants defined the term "exogenous nucleosomal polynucleotide" on page 10, [0030], as follows:

"As used herein, an "exogenous nucleosomal polynucleotide" is a polynucleotide which is transferred into a target cell but which has not been replicated in that host cell;"

6. Applicants defined the term "target nucleic acid sequence" on page 10, [0032], as follows:

"As used herein, the term "target nucleic acid sequence" refers to polynucleotide sequences suitable for recombination with a nucleosomal polynucleotide." Therefore the term is interpreted as any nucleic acid sequence.

7. Applicants defined the term "recombinase" on page 11, [0033], as follows:

"As used herein, "recombinase" refers to polypeptides having essentially all or most of the same functions, particularly the recombinase can: (i) properly bind to and position a nucleosomal polynucleotide to a homologous target and (ii) facilitate homologous recombination."

8. Applicants did not define the term "isolated recombinase", therefore any recombinase that is not contained within live cells is considered to anticipate this term.

9. Applicants did not define the term "Rad51 activity", therefore it is interpreted as any recombinase activity.

10. Applicants did not define the term "plasmid", therefore it is interpreted as any nucleic acid vector or virus.

Claim Rejections - 35 USC § 103

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

12. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and

invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

13. Claims 1, 5, 8, 10, 13, 16, 17, 19, 21 and 30-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ramdas et al. (Mol. Gen. Genet., vol. 249, pp. 336-348, 1995; cited in the previous office action), Ito et al. (Genes to Cells, vol. 2, pp. 593-600, 1997; cited in the previous office action), Wiesmuller et al. (J. Virol., vol. 70, pp. 737-744, 1996; cited in a previous office action), Jasin et al. (Cell, vol. 43, pp. 695-703, 1985) and Carroll et al. (Mol. Cell. Biol., vol. 6, pp. 2053-2061, 1986).

A) Claims 1 and 30 will be considered together in claim 1, since the only difference between the two claims is the limitation "nucleosomal" preceding "polynucleotide" in line 10 of claim 1.

Regarding claims 1 and 30, Ramdas et al. teach a method for promoting homologous recombination, the method comprising:

generating an exogeneous nucleosomal polynucleotide in vitro comprising (Abstract):

contacting an isolated relaxed polynucleotide, the isolated polynucleotide comprising a desired sequence to be recombined with purified histones to generate a nucleosomal polynucleotide comprising histones (page 337, paragraphs 3-5);

contacting, under conditions that support homologous recombination, the exogenous polynucleotide with a target nucleic acid, wherein the target nucleic acid comprises a nucleotide sequence homologous to the nucleosomal polynucleotide (page 338, third paragraph); and

contacting the nucleosomal polynucleotide and target nucleic acid with a recombinase comprising Rad51 associated activity (page 338, third paragraph; the immediately preceding step

and this step are performed simultaneously; recombinase with Rad51 activity is RecA, as evidenced by fourth paragraph on page 345).

Regarding claim 5, Ramdas et al. teach isolated RecA (page 338, third paragraph).

Regarding claim 8, Ramdas et al. teach contacting in vitro (page 338, third paragraph).

Regarding claim 10, Ramdas et al. teach exogenously provided nucleic acid (page 338, third paragraph).

Regarding claim 13, Ramdas et al. teach M13 plasmid, therefore they inherently teach coding sequences (page 337, fourth paragraph).

Regarding claim 16, Ramdas et al. teach core histones (page 337, fifth paragraph).

Regarding claim 17, Ramdas et al. teach a plasmid (page 337, fourth paragraph).

Regarding claims 19, 21 and 31, Ramdas et al. teach providing two different sequences, one of the M13 phage in the plasmid and the other of the ΦX174 plasmid (page 337, fourth paragraph; page 338, third paragraph; page 343, last paragraph; page 344, first paragraph; Fig. 9), therefore they inherently teach sequences which can introduce mutations into the M13 sequence.

B) Ramdas et al. do not teach using proteins that promote chromatin formation in the chromatin assembly reaction.

C) Regarding claims 1, 30, 32 and 33, Ito et al. teach several proteins the addition of which promotes chromatin assembly with proper spacing of nucleosomes in an ATP-dependent reaction, such as ACF and NAP1 (Table 1; page 596, second paragraph; page 597, paragraphs 3-7; page 598, paragraphs 1-3).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used the proteins which promote chromatin assembly of Ito et al. in the method of investigation of homologous recombination of Ramdas et al. The motivation to do so is provided by

Ito et al., who state that the chromatin assembled using ACF, for example, achieves periodically-spaced nucleosomes in reconstituted chromatin, in a fashion analogous to cell extracts (page 597, third and fourth paragraph). Therefore, one of ordinary skill in the art would have been motivated to use the additional proteins in order to achieve chromatin structure resembling in vivo structure, so that the studies of recombination would provide results meaningful to the mechanisms occurring in vivo.

D) Neither reference teaches performing the contacting of nucleosomal polynucleotides with target nucleic acids contained within a cell.

E) However, it would have been *prima facie* obvious to one of ordinary skill in the art to have used intact cells for performing homologous recombination between exogenous nucleic acid targets with a high expectation of success. The motivation to do so would have been that endogenous recombinases present within a cell could be used to provide recombination system, without the need for exogenous recombinase. Further, such a system would allow studies of the effects of different factors on recombination within different cell types. The expectation of success is provided by the following references:

i) Wiesmuller et al. teach homologous recombination between exogenous SV40 minichromosomes incorporated into within monkey cells (Abstract; page 737, last paragraph; page 738, paragraphs 2-4 and 10; page 739, second and third paragraphs).

ii) Jasin et al. similarly reported successful homologous recombination events between exogenous and endogenous SV40 minichromosomes within COS cells (Abstract; page 695, paragraphs 3-5; page 696, first paragraph; page 697, third and fourth paragraphs; Fig. 1 and 2).

iii) Carroll et al. teach homologous recombination between λ phage circular and linear molecules with Xenopus laevis oocytes (Abstract; Fig. 1; page 2054, paragraphs 4-11; page 2055).

14. No claims are allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to TERESA E. STRZELECKA whose telephone number is (571)272-0789. The examiner can normally be reached on M-F (8:30-5:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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